

WHAT IS CLAIMED IS:

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1. A combination, comprising:
a plurality of capture agents, wherein each capture agent
specifically binds to a polypeptide; and
- 5 a plurality of oligonucleotides that each comprise a sequence
of nucleotides that encodes a preselected polypeptide,
wherein:
the preselected polypeptides encoded by the oligonucleotides
comprise the polypeptides to which the capture agents bind; and
- 10 the oligonucleotides are single-stranded, double-stranded or
partially double-stranded.
2. The combination of claim 1, wherein the capture agents are
antibodies, and the preselected polypeptides comprise epitopes to which
the capture agents bind.
- 15 3. The combination of claim 1, wherein the capture agents are
arranged in an array.
4. The combination of claim 2, wherein the antibodies are
arranged in an array.
5. The combination of claim 1, wherein the capture agents are
20 linked directly or indirectly to a solid support.
6. The combination of claim 2, wherein the antibodies are
linked directly or indirectly to a solid support.
7. The combination of claim 5, wherein the support is
particulate.
- 25 8. The combination of claim 3, wherein the array is
addressable.
9. The combination of claim 2, wherein the array is
addressable.
10. The combination of claim 7, wherein the particles are
30 optically encoded.

11. The combination of claim 1, wherein each of the oligonucleotides comprises at least two regions, wherein the regions are a divider region that contains a sequence of nucleotides that comprise a sequence unique to a target library, and an 5 epitope-encoding region that encodes a sequence of amino acids to which a capture agent in the collection binds.

12. The combination of claim 11, wherein the divider region is 3' of the epitope-encoding region.

13. The combination of claim 11, wherein the divider and epitope 10 regions comprise at least about 10 nucleotides.

14. The combination of claim 13, wherein the divider and epitope regions comprise at least about 15 nucleotides.

15. The combination of claim 13, wherein each of the oligonucleotides further comprises a common region, wherein the 15 common region is shared by each of the oligonucleotides in the set, and is of a sufficient length to serve as a unique priming site for amplifying nucleic acid molecules that comprise the sequence of nucleotides that comprises the common region.

~~Sub 12~~ 16. the combination of claim 15, wherein the common region is 20 3' of the epitope-encoding region and/or of the divider region.

17. The combination of claim 1, wherein each oligonucleotide comprises a plurality of preselected polypeptides to which the capture agents bind.

18. The combination of claim 17, wherein the plurality is three.

25 19. The combination of claim 1, wherein the capture agents are immobilized at discrete loci on a solid support, wherein the capture agents at each loci specifically bind to one of the preselected polypeptides.

20. The combination of claim 19, wherein the capture agents are antibodies; and the preselected polypeptides comprise an epitope or 30 plurality thereof to which the antibodies bind.

21. The combination of claim 1 that comprises from 3 up to 10^6 capture agents that specifically bind to different polypeptides.

22. The combination of claim 2 that comprises from 3 up to 10^6 antibodies that specifically bind to different epitopes.

5 23. The combination of claim 15, wherein the length of each of the divider, epitope and common regions is at least about 14 nucleotides.

24. The combination of claim 1, wherein the oligonucleotides comprise formula:

10 $5'-E_m-3'$
wherein:
each E encodes a sequence of amino acids to which a capture agent binds, wherein each such sequence of amino acids is unique in the set;
m is, independently, an integer of 2 or higher.

15 25. The set of oligonucleotides of claim 24, wherein each oligonucleotide further comprises a common region C, and comprises formula:

5' C-E_m 3',
wherein the common region is shared by each of the

20 oligonucleotides in the set, and is of a sufficient length to serve as a unique priming site for amplifying nucleic acid molecules that comprise the sequence of nucleotides that comprises the common region.

26. The combination of claim 1, wherein the oligonucleotides comprise formula:

25 $5'-D_n-E_m-3'$
wherein:
each D is a unique sequence among the set of oligonucleotides and contains at least about 10 nucleotides;
each E encodes a sequence of amino acids to which a capture

30 agent binds, wherein each such sequence of amino acids is unique in the set;

each of n and m is, independently, an integer of 2 or higher.

27. The combination of claim 16, wherein the capture agents are antibodies; and the unique sequence of amino acids comprises an epitope.

28. The combination of claim 27, wherein m is the number of 5 antibodies with different epitope specificity in the combination and n is from about 2 up to and including 10^6 .

29. The combination of claim 26, wherein m is the number of capture agents with different epitope specificity in the combination and n is from about 2 up to and including 10^6 .

10 30. The combination of claim 28, wherein n is from about 2 to about 10^4 , inclusive.

31. The combination of claim 29, wherein n is from about 2 to about 10^4 , inclusive.

15 32. The combination of claim 29, wherein n is from about 2 to about 10^2 , inclusive.

33. The combination of claim 2 that comprises up to about 10^3 antibodies.

34. The combination of claim 11, wherein the length of each of the divider and epitope regions is independently at least about 14 20 nucleotides.

35. The combination of claim 11, wherein the length of each of the divider and epitope regions is independently at least about 16 nucleotides.

25 36. The combination of claim 1, wherein the oligonucleotides are single-stranded primers.

37. The combination of claim 1, wherein the oligonucleotides are double-stranded.

30 38. A set of oligonucleotides comprising formula:
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 $5'-D_n-E_m-3'$
wherein:

each D is a unique sequence among the set of oligonucleotides and contains at least about 10 nucleotides;

each E encodes an a sequence of amino acids that comprises epitope;

5 each epitope is unique in the set;

each epitope is a sequence to which a capture agent binds;

each of n and m is, independently, an integer of 2 or higher; and the oligonucleotides are single-stranded, double-stranded, and/or partially double-stranded.

10 39. The set of oligonucleotides of claim 38, wherein $m \times n$ is between about 10 to about 10^{12} , inclusive.

40. The set of oligonucleotides of claim 38, wherein $m \times n$ is between about 10 to about 10^9 , inclusive.

41. The set of oligonucleotides of claim 38, wherein $m \times n$ is 15 from about 10 up to about 10^6 , inclusive.

42. The set of oligonucleotides of claim 38, wherein each oligonucleotide further comprises a common region C, and comprises formula:

5' C-D_n-E_m 3',

20 wherein the common region is shared by each of the oligonucleotides in the set, and is of a sufficient length to serve as a unique priming site for amplifying nucleic acid molecules that comprise the sequence of nucleotides that comprises the common region.

43. A combination of sets of oligonucleotides, comprising the set 25 of oligonucleotides of claim 38 and another set of oligonucleotides of formula: 5' C-D_n 3', wherein C is a sequence of nucleotides common to all oligonucleotides in the set.

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 44. A combination of sets of oligonucleotides, comprising the set of oligonucleotide of claim 42 and another set of oligonucleotides of formula:

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5' C-D_n 3' , wherein C is a sequence of nucleotides common to all oligonucleotides in the set.

45. A combination of sets of oligonucleotides, comprising the sets of oligonucleotides of claim 43 and another set of oligonucleotides of formula:

5' C-E_p-FA_s 3', wherein:

E_p is one of the E₁-E_m epitope-encoding oligonucleotides;

FA comprises a sequence of nucleotides that contains a sufficient portion of E_p to amplify nucleic acids, if it is used as a primer, that contains E_p, but insufficient to encode the epitope encoded by E_m; each of s and p is an integer of to 2 or higher up to m.

46. A combination of sets of oligonucleotides, comprising the sets of oligonucleotides of claim 44 and another set of oligonucleotides of formula:

15 5' C-E_p-FA_s 3', wherein:

E_p is one of the E₁-E_m epitope-encoding oligonucleotides;

each FA_s comprises a sequence of nucleotides that contains a sufficient portion of E_p to amplify nucleic acids, if it is used as a primer, that contains E_p, but insufficient to encode the epitope encoded by E_m;

20 each of s and p is an integer of to 2 or higher up to m.

47. A combination of sets of oligonucleotides, comprising the sets of oligonucleotides of claim 45 and another set of oligonucleotides of formula:

5'C-FB_z-3', wherein:

25 z is an integer from 2 to M;

C is a region common to each oligonucleotide in the set;

each FB_z comprises a sequence of nucleotides that contains at least a sufficient portion of and each E_p to amplify nucleic acids containing such E_p.

48. A combination of sets of oligonucleotides, comprising the sets of oligonucleotides of claim 46 and another set of oligonucleotides of formula:

5' -FB_z-3', wherein:

5 z is an integer from 2 to M,
each FB_z comprises a sequence of nucleotides that contains at least a sufficient portion of and each E_p to amplify nucleic acids containing such E_p.

49. A system for sorting collections of molecules, comprising:

10 a) a combination of claim 1; and
b) a computer system with software for analyzing results of sorts.

50. A system for sorting collections of molecules, comprising:

15 a) a combination of claim 2; and
b) a computer system with software for analyzing results of sorts.

51. The system of claim 49, further comprising a reader for detecting binding to capture agents in the collection.

52. The system of claim 51, wherein the reader comprises an imaging system.

53. The system of claim 50, wherein a computer system stores data and/or assesses data collected by the reader.

54. The system of claim 52, wherein the imaging system is a charge coupled device (CCD) or an array of photodiodes.

25 55. A plurality of arrays, comprising:
a support for linking capture agents; and
a plurality of arrays of capture agents linked to the support,
wherein:
each capture agent specifically binds to a preselected
30 polypeptide;

the capture agents are immobilized at discrete loci, wherein the capture agents at each loci specifically bind to one of the preselected polypeptides; and

each array in the plurality is a replica of the others.

5 56. The plurality of arrays of claim 55, wherein the capture agents are antibodies; and the preselected polypeptides comprise epitopes to which the antibodies specifically bind.

10 57. The plurality of arrays of claim 55, wherein each array is separated from the other arrays by a hydrophobic region or a physical barrier.

58. The plurality of arrays of claim 56, wherein the support is gelatin coated or coated with silicon or derivatized silicon.

59. The set of oligonucleotides of claim 38, wherein the capture agent is an antibody.

15 60. A method for creating a tagged library, comprising: incorporating each one of the set of oligonucleotides of claim 38 into a nucleic acid molecule in a library of nucleic acid molecules to create a tagged library.

61. A library produced by the method of claim 60.

20 62. The method of claim 60, wherein each oligonucleotides further comprises a common region and has the formula: 5' C-D_n-E_m- 3', wherein C is a region common to each oligonucleotide.

25 63. A method for creating a tagged library, comprising: incorporating each one of a set of oligonucleotides that each comprises a region E_m into a nucleic acid molecule in a library of nucleic acid molecules to create a tagged library, wherein:

the oligonucleotide comprises the formula:

5'-E_m- 3';

30 each E encodes a sequence of amino acids to which a capture agent specifically binds;

each such sequence of amino acids is unique in the set; and

m is, independently, an integer of 2 or higher.

64. The method of claim 63, wherein:

E encodes an epitope to which an antibody binds; and the capture agents are antibodies.

5 65. A library produced by the method of claim 63.

66. A library produced by the method of claim 64.

67. A method for screening a nucleic acid library, comprising:

a) creating a tagged library by the method of claim 63;

b) translating the library or a sublibrary thereof;

10 b) contacting proteins from the translated library or sublibrary with a collection of capture agents to produce complexes between the tagged proteins and capture agents, wherein:

each of the capture agents specifically binds to a polypeptides encoded an E_m ; and

15 each of the capture agents is identifiable;

c) screening the complexed capture agents to identify those that have bound to a translated protein of interest, thereby identifying the E_m that is linked to the protein of interest.

68. The method of claim 67, further comprising:

20 d) isolating the nucleic acid molecules encoding the E_m linked to the protein of interest.

69. The method of claim 67, wherein the capture agents are antibodies.

25 70. The method of claim 67, wherein the capture agents are arranged in a positional array.

71. The method of claim 67, wherein the capture agents are attached to identifiable particles.

26 72. The method of claim 72, wherein the particles are optically encoded.

30 73. The method of claim 67, wherein each oligonucleotide from which the library is created comprises the formula: 5' D_n-E_m- 3'.

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74. The method of claim 67, wherein each oligonucleotide from which the library is created comprises the formula: 5' C-D_n-E_m- 3'.

75. A method for nested sorted, comprising:

- a) creating tagged collections of nucleic acid molecules by
- 5 incorporating each one of the set of oligonucleotides of claim 38, at one end of each nucleic acid molecule to create a master collection comprising N members;
- b) amplifying each of n samples with a primer that comprises D_n to produce n sets of amplified nucleic acid reactions, wherein each reaction
- 10 comprises amplified sequences that comprise a single D_n and all of the E_m's;
- c) translating each sample to produce n translated samples;
- d) contacting proteins from each translated reaction with one of n collections of capture agents to produce complexes thereof, wherein each
- 15 of the capture agents in the collection specifically reacts with a sequence of amino acids encoded by an E_m; and each of the antibodies can be identified;
- e) screening the complexes to identify those that have bound to a protein of interest, thereby identifying the E_m and D_n that is linked to
- 20 nucleic acid molecules that encode the protein of interest.

76. The method of claim 75, wherein the capture agents are antibodies.

77. The method of claim 75, further comprising, amplifying the nucleic acid in the sample that contains the identified E_m, D_n with a set of

25 primers that each contains a portion of E_m sufficient to amplify the linked nucleic acid, but insufficient to reintroduce all E_m, wherein each primer comprises the formula E_m-FA_s, where each of m and s is an integer of 2 or higher up to M, the number of epitope tags,

thereby introducing a different one of the E_m sequences into the

30 nucleic acid to produce a sublibrary that again contains all of the E_m sequences.

78. The method of claim 77, further comprising:
translating the nucleic acids in the sublibrary;
contacting with the collection of capture agents with the translated
proteins;

5 screening and identifying the capture agents that bind to the
sequence of amino acids encoded by E_m linked to the protein of interest,
thereby identifying the E_m ; and
specifically amplifying the identified E_m tag in the sublibrary to
produce the nucleic acid that encodes a protein of interest.

10 79. The method of claim 77, wherein the collection of capture
agents comprises an addressable array.

80. The method of claim 77, wherein the capture agents are
identifiably labeled.

81. The method of claim 79, wherein the capture agents are
15 linked to optically encoded particulate supports.

82. The method of claim 81, wherein the label is colored,
chromogenic, luminescent, chemical, fluorescent or electronic.

83. The method of claim 75, wherein the oligonucleotides in step
a) have the formula: 5' C-D_n-E_m 3'.

20 84. The method of claim 75, wherein the nucleic acid encoding
the E tags are introduced by PCR amplification or by ligation to the
nucleic acid in the library optionally followed by amplification.

85. The method of claim 84, wherein the oligonucleotides in step
a) are in plasmids.

25 86. The method of claim 75, wherein the collection of capture
agents are antibodies that comprise an addressable array.

87. The method of claim 86, wherein addressing is effected
identifiably labeling the antibodies.

Sub A17 88. The method of claim 87, wherein the label optical,
30 chromogenic, luminescent, chemical, fluorescent or electronic.

89. The method of claim 86, wherein the antibodies are linked to a support that is labeled with a bar code or a radio-frequency tag.

90. The method of claim 86, wherein the antibodies are linked to a support that is a colored bead.

5 91. A collection of molecules, wherein each molecule is labeled with one of a set of epitope tags, wherein:

each epitope tag includes a divider region selected from among n divider regions, and an epitope region that is selected from among m epitopes;

10 each divider region contains at least about three amino acids; each epitope region contains a sufficient number of amino acids to constitute an epitope to which an antibody can specifically bind.

92. The collection of claim 91, wherein there are $m \times n$ different epitope tags.

15 93. The combination of claim 1, that comprises from about 30 up to about 10^4 capture agents.

Sub A 94. The combination of claim 29, n is from about 2 up to and including 10^5 .

95. The combination of claim 29, wherein n is from about 2 to 20 about 10^3 , inclusive.

96. A method of sorting nucleic acid libraries, comprising: linking a sequence of nucleotides that encodes an epitope to members of a nucleic acid library; translating the library to produce the encoded proteins with linked epitope tags;

contacting the translated library with linked epitope tags with a collection of capture agents that specifically bind to the epitopes.

25 97. The method of claim 96, wherein the collection of capture agents comprises an array.

Sub A 98. The method of claim 96, wherein the collection of capture agents comprise antibodies.